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(54) Title: RECOVERY AND RECYCLING OF CHIRAL TARTARIC ACID RESOLVING AGENTS

(57) Abstract: A process for the recovery of substituted tartaric acid resolving agents from resolution process liquors comprising organic solvents, wherein the substituted tartaric acid derivatives are neutralized by adding a base, extracted into an aqueous phase and crystallised from the aqueous phase by addition of a mineral acid in the presence of an organic solvent.

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# Recovery and recycling of chiral tartaric acid resolving agents

## Specification

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This invention relates to a novel process for the recovery of chiral substituted tartaric acid resolving agents from process liquors in a form of sufficient purity to enable their recycle in the corresponding resolution process.

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Chemical processes for the synthesis of optically active amine compounds frequently use optically active organic acid resolving agents to allow the required enantiomer to be preferentially crystallised as a salt with the resolving agent. The required  
15 optically active amine can then be regenerated by basification of the salt.

Particular examples of such resolution processes are found in the synthesis of N-benzylpiperidines and tetrahydropyridine  
20 derivatives which are useful intermediates in the synthesis of (-)-trans-4-(4-fluorophenyl)-3-(3,4-methylenedioxyphenoxymethyl) piperidine and its salts, a drug having anti-depressive effects.

One such process is disclosed in patent WO 98/01424, which  
25 describes the resolution of a racemic tertiary amine intermediate to form the optically pure salt of the required absolute configuration with a substituted tartaric acid resolving agent. The optically active amine is regenerated by reaction of the salt with a suitable base to give the substituted tartaric acid  
30 as a salt in aqueous solution as a byproduct.

In WO 01/46148 a process for the manufacture of (-)trans piperidine carbinols is disclosed wherein the racemic piperidine carbinol is contacted with (-)ditoluol tartaric acid, followed  
35 by isolation of the crystalline salt and regeneration of the ditoluoltartaric acid by addition of an aqueous inorganic base.

According to the Japanese laid open application No. 09176115 optically active tartaric acid derivatives can be recovered  
40 from a resolving process for optically active aminopyrrolidones by treatment of the salts with alkalis in water, followed by extraction of the aqueous layer with organic solvents and addition of mineral acids to the aqueous layer.

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Examples of resolving agents used in such resolution processes include (+)-di-O,O'-toluoyl-(D)-tartaric acid, (-)-di-O,O'-toluoyl-(L)-tartaric acid, (+)-di-O,O'-benzoyl-(D)-tartaric acid, (-)-di-O,O'-benzoyl-(L)-tartaric acid. Examples of such 5 structures are shown in figure 1.

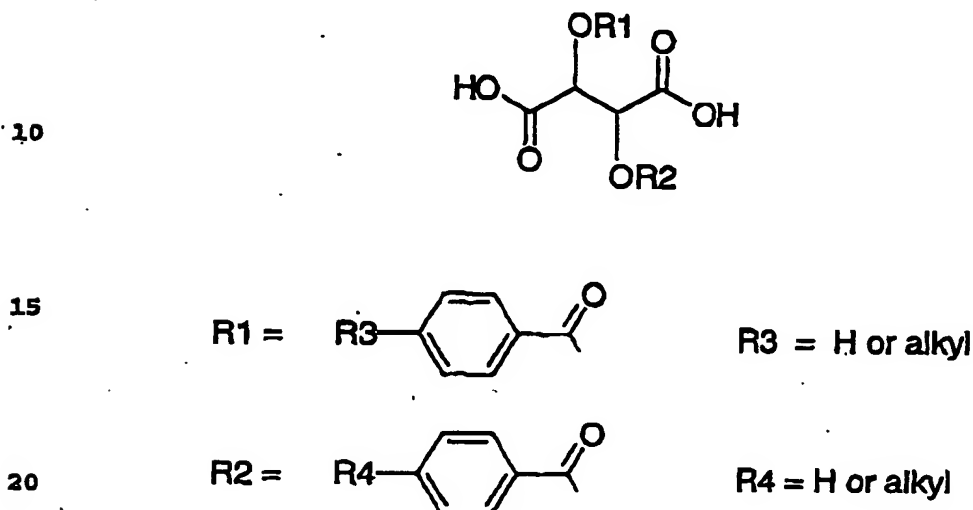


Figure 1

25 Such resolving agents are typically expensive to manufacture or purchase.

Previous to this invention, methods used to recover substituted tartaric acid resolving agents have been found to give poor 30 yields and low purity due to the prevalence of unwanted esterification, transesterification, or de-esterification reactions. The poor efficiency of previously used recovery processes are also the result of the need to extract the substituted tartaric acid into a water-immiscible organic 35 solvent, then to crystallise it from a different solvent with consequent extended time for distillation. Such solvent exchange operations increase the losses due to the unwanted side reactions referred to above.

40 It is an object of the present invention to provide an improved process for the recovery of substituted tartaric acid resolving agents from resolution mother liquors comprising organic solvents.

45 We have found that this object is achieved by a process wherein the substituted tartaric acid derivatives are neutralised by adding a base, extracted into an aqueous phase and crystallised

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from the aqueous phase by addition of a mineral acid in the presence of a water soluble organic co-solvent.

This invention relates to an efficient method for recovery of the substituted tartaric acid resolving agent from the resolution mother liquor or from the aqueous phase from regeneration of the chiral salt in a form which may be recycled for use in further resolution reactions. Accordingly, the term "mother liquor" as used herein means the process liquor from the resolution process as well as the process liquor of the regeneration process.

Typically such process liquors comprise one or more organic solvents in addition to the resolving agent and the optically active amine. Typical organic solvents used for the resolving process are ketones, e.g. acetone, alcohols such as for instance methanol, aromatic hydrocarbons, e.g. toluene, ethers such as for instance tetrahydrofuran or mixtures thereof. Preferably the organic solvent is only poorly miscible with water or water immiscible, if not a water miscible solvent needs to be distilled off and replaced by a poorly water miscible or immiscible solvent, e.g. toluene.

In this invention the mother liquor may be reacted, optionally after solvent exchange, with a suitable base to give a salt of the substituted tartaric acid resolving agent which is dissolved in water to allow separation from organic by-products which may be dissolved in a water immiscible organic solvent. The aqueous phase obtained contains the substituted tartaric acid resolving agent as its salt with the base and is similar in composition to the solution obtained from the regeneration of the optically active amine from its salt with the resolving agent.

The base used for neutralisation of the amine salt of the substituted tartaric acid resolving agent may be a hydroxide, carbonate or hydrogen carbonate salt of an alkali or alkaline earth metal or optionally substituted ammonia. Preferably the base is sodium or potassium carbonate or hydrogen carbonate or ammonia. More preferably the base is sodium hydrogen carbonate. The base is preferably added in the form of an aqueous solution. The concentration of the base in the solution depends on the type of base used.

The co-solvent added to the aqueous solution containing the substituted tartaric acid resolving agent may be any water soluble or partly watersoluble organic solvent, preferably a C<sub>1</sub> to 10-alcohol, more preferably 2-butanol.

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The mineral acid may be any strong acid, preferably sulphuric, phosphoric, hydrochloric, hydrobromic or nitric acid, more preferably hydrochloric acid. The mineral acid is added in amounts sufficient to recover tartaric acid derivative in the form of the free acid.

The recovery of the tartaric acid derivatives is typically carried out at 20 to 50°C. The product is filtered off and dried, typically under reduced pressure.

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The process according to the present invention is particularly advantageous in the recovery of tartaric acid resolving agents from mother liquors in the manufacture of optically pure (+)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine.

Unexpectedly it has been discovered that addition of a suitable organic solvent together with a mineral acid results in crystallisation of the substituted tartaric acid resolving agent directly from the aqueous mixture, without the need for phase separation or solvent exchanges, and in a manner which is reproducible on a commercial scale.

A particularly advantageous feature of the present invention is the isolation of substituted tartaric acid resolving agent in a crystalline form of suitable purity for reuse in a resolution reaction without additional purification. The substituted tartaric acid resolving agent is typically crystallised as a solvate with the co-solvent used, of a purity in excess of 95% excluding the residual solvent. The optical purity of the substituted tartaric acid resolving agent is not significantly affected by the recovery process.

The present invention includes use of such a solvate of the substituted tartaric acid resolving agent in a resolution reaction.

#### Examples

##### 40 Example 1

A solution (16.1 litres) containing (+)-di-O,O'-toluoyl-(D)-tartaric acid (about 1106g) and 1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine dissolved in methanol was concentrated by distillation of methanol and diluted with toluene (5.0kg). The mixture was warmed to 40°C and 1 M sodium hydrogen carbonate solution (6.3 litres) was added slowly. The

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mixture was stirred for 30 minutes then the lower aqueous phase containing (+)-di-O,O'-toluoyl-(D)-tartaric acid as its disodium salt was separated off. The organic phase was stirred with water (1.8 litres) at 40°C for 30 minutes. The lower aqueous phase was  
5 separated off. The aqueous phases were combined and 2-butanol (2.5 litres) was added. The mixture was warmed to 40°C and hydrochloric acid (552 ml) was added slowly. The mixture was cooled to 10°C and stirred for 30 minutes then the solid (+)-di-O,O'-toluoyl-(D)-tartaric acid was collected by filtration and washed  
10 twice with water (2 x 2.2 litres). The damp solid was dried at 50°C under reduced pressure. (+)-Di-O,O'-toluoyl-(D)-tartaric acid (1270g) was obtained as its 2-butanol solvate, HPLC assay 72%/28% retained solvent, 83% of theory.

## 15 Example 2

(+)-1-benzyl-3-hydroxymethyl-4-(4-fluorophenyl)-1,2,3,6-tetrahydropyridine (+)-di-O,O'-p-toluoyl-D-tartrate (1.8kg) was suspended in toluene (6.9 litres). The mixture was warmed to  
20 35°C and 1 M sodium hydrogen carbonate solution (6.6 litres) was added slowly. The mixture was stirred at 35 to 40°C for 2 hours then the lower aqueous phase containing (+)-di-O,O'-toluoyl-(D)-tartaric acid as its disodium salt was separated off. The organic phase was stirred with water (4.4 litres) at 35 to  
25 40°C for 30 minutes. The lower aqueous phase was separated off. The aqueous phases were combined and 2-butanol (2.9 litres) was added. The mixture was warmed to 40°C and hydrochloric acid (720 ml) was added slowly. The mixture was cooled to 10°C and stirred for 30 minutes then the solid (+)-di-O,O'-toluoyl-(D)-  
30 tartaric acid was collected by filtration and washed twice with water (2 x 1.8 litres). The damp solid was dried at 50°C under reduced pressure (10-300 mbar). (+)-Di-O,O'-toluoyl-(D)-tartaric acid (1310g) was obtained as its 2-butanol solvate, HPLC assay 76%/24% retained solvent, 98% of theory.

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## Claims

1. A process for the recovery of substituted tartaric acid  
5 resolving agents from resolution process liquors comprising organic solvents, wherein the substituted tartaric acid derivatives are neutralised by adding a base, extracted into an aqueous phase and crystallised from the aqueous phase  
10 by addition of a mineral acid in the presence of an organic solvent.
2. A process according to claim 1 wherein the substituted  
tartaric acid resolving agent is chosen from (+)-di-O,O'-  
15 toluoyl-(D)-tartaric acid, (-)-di-O,O'-toluoyl-(L)-tartaric acid, (+)-di-O,O'-benzoyl-(D)-tartaric acid, or (-)-di-O,O'-benzoyl-(L)-tartaric acid.
3. A process according to any of the preceding claims wherein  
20 the base is added as an aqueous solution.
4. A process according to any of the preceding claims wherein  
the substituted tartaric acid resolving agent is neutralised  
25 by a hydroxide, carbonate or hydrogen carbonate salt of an alkali or alkaline earth metal or optionally substituted ammonia.
5. A process according to any of the preceding claims wherein  
the substituted tartaric acid resolving agent is crystallised  
30 from aqueous solution in the presence of an organic solvent which is a C<sub>1</sub> to 10-alcohol.
6. A process according to any of the preceding claims wherein  
the organic solvent is 2-butanol.
- 35 7. A process according to any of the preceding claims wherein the mineral acid is hydrochloric acid, hydrobromic acid, or sulfuric acid.
8. A process according to any of the preceding claims wherein  
40 the mineral acid is hydrochloric acid.
9. A process according to any of the preceding claims wherein  
the substituted tartaric acid resolving agent is crystallised  
45 in the form of a solvate with the co-solvent.

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10. Substituted tartaric acid resolving agents in the form of a solvate, obtained according to a process according to any of the preceding claims.

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/EP 02/12494

## A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07B C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, WPI Data, EPO-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DATABASE CA 'Online!            CHEMICAL ABSTRACTS SERVICE, COLUMBUS,            OHIO, US;            SAKAI, TOSHIHITO ET AL: "Preparation of            optically-active            N-benzyl-3-aminopyrrolidine by resolution            with optically-active tartaric acid            derivatives and recovery of the resolving            agents"            retrieved from STN            Database accession no. 127:121629 CA            XP000223197            abstract            &amp; JP 09 176115 A (KOEI CHEMICAL CO., LTD.,            JAPAN) 8 July 1997 (1997-07-08)            see JP-translation</p>	1-10

☐ Further documents are listed in the continuation of box C.☐ Patent family members are listed in annex.

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Date of the actual completion of the international search

6 March 2003

Date of mailing of the international search report

12/03/2003

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Information on patent family membersInternational Application No  
**PCT/EP 02/12494**

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 9176115	A	08-07-1997	NONE

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